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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,533	ARINI ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *81-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/08/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 81-90 are pending in the application.

[2] Applicants' amendment to the claims, filed April 08, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's amendment to the specification, filed April 08, 2004, is acknowledged.

[4] Receipt of an information disclosure statement (IDS), filed April 08, 2004, is acknowledged. All cited references have been considered by the examiner and a copy of the IDS is attached to the instant Office action.

[5] Applicant's arguments filed April 08, 2004 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Specification

[7] In view of applicants' amendment to the specification, the objection to the specification as set forth in item [12] of the Office action mailed October 06, 2003 is withdrawn.

[8] The use of trademarks has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112, Second Paragraph

[9] Claims 81-90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 81 (claims 82-84, 86, and 88-90 dependent therefrom) is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step(s) is/are: a step of culturing the eukaryotic cell line for production of the catalytically active tc-uPA. According to the instant specification, the following steps are required for the production of the desired level of tc-uPA: "a) culturing genetically manipulated CHO cells transfected with the pre-prouK cDNA or gene in a culture media comprising alkanoic acids or their derivatives or salts thereof" and "b) continuing said culture for a period of time of at least 24 hours" (specification, page 6). In view of the specification (page 6), a skilled artisan would recognize that a step of culturing the eukaryotic cell line for a time of at least 24 hours in the presence of an alkanoic acid is essential for the production of the catalytically active tc-uPA at the desired level, i.e., 95% tc-uPA. It is

suggested that, for example, applicants incorporate the essential step into the claimed process.

[b] Claims 85 and 87 recite the limitations "cell line is grown." There is insufficient antecedent basis for this limitation in the claims as the method of claim 81 does not include a step of growing the cell line. It is suggested that applicants clarify the meaning of the claims.

[c] The rejection of claim 87 under 35 U.S.C. 112, second paragraph, is maintained for the reasons of record as set forth in item [15] of the Office action mailed October 06, 2003 and for the reasons stated below.

In summary, the claim is rejected as the Declaration under 37 CFR 1.132, filed May 15, 2003 indicates that, at least under the conditions used in the experiment, a culturing time of at least 96 hours is required to produce the requisite 95% catalytically active tc-uPA (see Figure 2) and thus, it is unclear as to how a culturing time of less than 96 hours will allow for the production of the required 95% catalytically active tc-uPA.

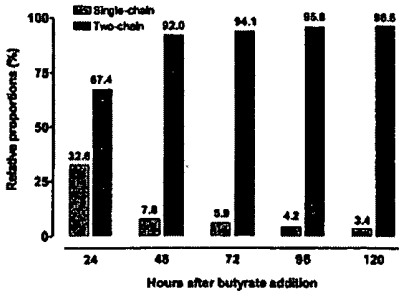
Applicants argue the experiment reported in the Declaration does not demonstrate that under all possible conditions and variables it would always require 96 hours of culturing to reach the recited 95% level of uPA and that the examiner's interpretation of the data is in error. Applicants argue that the purpose of 35 USC 112, second paragraph, is to point out the invention such that one of skill can recognize the scope of the claimed invention and that the claim serves this purpose and the rejection should be withdrawn. Applicants' argument is not found persuasive.

Although not indicated in the specification, based upon applicants' arguments, it would appear that particular conditions and variables are essential for the claimed method to achieve the desired 95% level of uPA after only 48 hours of cell culture. However, these essential conditions and variables are not present in the claim. Thus, the claim has omitted essential elements that are required to practice the claimed invention. See MPEP § 2172.01. It is suggested that, for example, applicants amend the claim to recite those conditions and variables that are required to achieve the desired 95% level of uPA after only 48 hours of cell culture.

Claim Rejections - 35 USC § 112, First Paragraph

[10] The scope of enablement rejection of claims 81-90 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth in item [16] of the Office action mailed October 06, 2003 and for the reasons stated below.

In summary, the claims are rejected because the specification, while being enabling for a process for producing at least 95% catalytically active tc-uPA wherein the eukaryotic cell line is cultured for a time of at least 96 hours, does not reasonably provide enablement for a process for producing at least 95% catalytically active tc-uPA wherein the eukaryotic cell line is cultured for a time of less than 96 hours.



Applicants argue that the results of the experiment reported in Figure 2 of the Declaration under 37 CFR 1.132, filed May 15, 2003 (shown at right) are based on a single

experiment and are shown without their statistical significance. Applicants argue that variations, which were known to applicant, occur due to unavoidable experimental error and the selection of biological systems and cite additional sources of error that may contribute to experimental variability. Applicants argue that a 92% conversion was reached in 48 hours and that allowing for the expected experimental variability, a skilled artisan would assume that a 5% variation in the experiment would conform to even the most rigorous statistical rules and thus, a 5% error applied to the 92% value would place the 92% value within the 95% level of the claims. Applicants argue that the differences in the value given in the Declaration (92%) and the claimed 95% value is within the range of 3%, which is even lower than would be experimentally expected by a skilled artisan. Applicants' arguments are not found persuasive.

There is no dispute that variation in the results of any experiment – particularly those using biological systems – will occur when the experiment is reproduced. Applicants attempt to discount the evidence provided in the Declaration asserting that the discrepancy in the results obtained in the experiment of the Declaration are due to experimental error. Applicants are reminded that "[t]he arguments of counsel cannot take the place of evidence in the record." See MPEP 2145. Based on the statements of the declarant, it would appear that the results of the experiment are based on "sound experimental evidence," particularly as the declarant states, "[o]n the basis of these observations, I can assure that the assertions relative to the specific points described herein, and contained in the patent application, are true and supported by sound experimental evidence" (page 3, top of the Declaration). Thus, the Declaration filed

under 37 CFR 1.132 provides evidence that, at least under those conditions used in the disclosed experiment, a culturing time of at least 96 hours is required to obtain 95% catalytically active tc-uPA, which requires proteolytic conversion of sc-uPA to tc-uPA. The specification discloses the determination of those conditions that are "optimal" for tc-uPA production (Example 2, pages 14-16) and there is no indication that the experimental conditions used in the production of tc-uPA in the Declaration were any different from those that are considered to be "optimal" by applicants. Further, one of skill intending to obtain "sound experimental evidence" would recognize that in order to obtain such experimentally sound evidence, one would most likely use those conditions that were used in a previous experiment or would at least use those experimental conditions that are considered to be optimal rather than sub-optimal conditions.

Applicants argue that "[t]he 95% value which is set forth in claim 81 represents an average value that... ...is based on more than one experiment" (page 7, top of the response). However, applicants' argument is not commensurate in scope with the claim as there is no recited limitation in claim 81 that requires that the 95% level of catalytically active tc-uPA be an average value "based on more than one experiment." It should be noted that, even if the experiment of the Declaration were repeated, there is no indication that the resulting level of tc-uPA would be greater at the 48 or 72 hour mark. It is just as likely that the level of tc-uPA would be equal to or less than the level of tc-uPA shown at 48 or 72 hours of Figure 2 of the Declaration. As the results of the experiment disclosed in Figure 2 of the Declaration are asserted to be based on a single experiment, there is no way to statistically determine the level of experimental error of

the results, and thus it is unclear as to whether the experimental error is 5%, 10%, 15%, etc., for this particular experiment. Even assuming arguendo that the experimental error is 5%, it is noted that applicants have ignored the possibility that a 5% error applied to the 92% value at 48 hours of culturing could just as likely place the 92% value within an 87% (i.e., 92%-5%) level of catalytically active tc-uPA.

Citing MPEP 2164.08, applicants argue: 1) the examiner must consider the claim as a whole and not individual parts; 2) reasonable experimentation to practice an invention is allowed without causing a patent claim to be non-enabled; 3) the claims should not be limited to that which is found to work. Applicants further argue that it is well known that process conditions may be varied to influence rate and yield of reactions and the disclosure of actual results at 96 hours does not provide evidence that the claimed process cannot be accomplished in a lesser period of time. Applicants' arguments are not found persuasive.

In this case, the examiner has considered the claim as a whole and in light of the specification. In this case, there is no evidence in the specification that a culturing time of less than 96 hours will achieve the desired level of tc-uPA and based upon evidence provided by applicant in the form of a Declaration under 37 CFR 1.132, at least under those conditions used in the disclosed experiment, the specification does not enable the entire scope of the claimed process, particularly in light of the specification, which asserts that the process requires as few as 24 hours to achieve the desired result (see, e.g., page 6, middle). Applicants infer that under conditions other than those used in the experiment of the Declaration, a skilled artisan can achieve the desired result in less

than 96 hours of culturing (page 6, middle of the response). However, the only evidence of record indicates that at least 96 hours of culturing time is required to achieve the recited level of tc-uPA. While inoperative embodiments encompassed within the scope of a claim (such as that shown in Figure 2 of the Declaration for obtaining 95% catalytically active tc-uPA in less than 96 hours) do not render the claimed invention non-enabled, in this case, the specification fails to identify those conditions that are essential to enable one of skill in the art to achieve the desired 95% catalytically active tc-uPA in as little as 24 hours of cell culturing or in less than 96 hours of culturing. MPEP 2164.08(b) states, "[t]he standard [for determining whether inoperative embodiments render a claim non-enabled] is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." It is the examiner's position that undue experimentation is required for a skilled artisan to determine those conditions under which the claimed process will successfully achieve the desired result in less than 96 hours of culture time, particularly in view of the broad scope of the claims, which encompasses any culturing time, the lack of guidance and working examples demonstrating that the desired level of tc-uPA can be achieved in as little as 24 hours of culture time, the high level of unpredictability as evidenced by the failure of the experiment shown in the Declaration to achieve the desired level of tc-uPA in under 96 hours, and the amount of experimentation required to determine those specific conditions for achieving the desired level of tc-uPA under a given culturing time and those that are inoperable.

Applicants argue the examiner has not acknowledged that when the Wands decision is applied to the facts of the instant rejection, a finding of proper enablement is required. Applicants argue the instant situation is analogous to that of Wands in that the instant rejection relies upon an operable experiment as the sole basis on which to argue that the claimed method requires 96 hours to achieve the desired level of tc-uPA. Applicants argue that because this single experiment was within the scope of claimed processes and did not include all conditions and materials within the claims, there is no basis to conclude that 96 hours is the minimum time required to reach the 95% level of tc-uPA. Applicants' argument is not found persuasive.

Applicants attempt to demonstrate enablement of the full scope of the claimed invention by analogy to Wands. While there is no dispute that the results of the experiment of Figure 2 of the Declaration demonstrated that the process will achieve the desired level of tc-uPA by culturing for at least 96 hours, this evidence also demonstrates that this level of tc-uPA cannot be achieved under all condition that are encompassed by the instant claims, including a culturing time of as little as 24 hours as asserted in the specification (page 6). Thus, the full scope of the claimed process is not enabled by the instant specification. In the case of Wands, it is noted that the court found that "Wands... ...was successful each time in making at least one antibody that satisfied all of the claim limitations." However, in this case, as evidenced by the Declaration, the process is not successful on each attempt for achieving the level of tc-uPA at a culturing time of as little as 24 hours, which is encompassed by the scope of the claims. As such, in view of the Factors of In re Wands (as detailed in the Office

action mailed October 06, 2003) and for the reasons stated above, the full scope of the claimed process is not enabled by the instant specification.

Claim Rejections - 35 USC § 103

[11] The rejection of claims 81-85 and 87-89 under 35 U.S.C. 103(a) as being unpatentable over Okabayashi et al. (Cell Struc Funct 14:579-586) in view of the state of the art as represented by Zang et al. (Biotechnology (NY) 13:389-392) is maintained for the reasons of record as set forth in item [19] of the Office action mailed October 06, 2003 and for the reasons stated below.

Applicants argue that the claimed process is for producing a high level of tc-uPA, not for the purpose of increasing the total amount of urokinase, that sc-uPA and tc-uPA are not the same molecule based on their distinct physico-chemical properties, and that attempts at recombinantly producing tc-uPA "is still an open question." Applicants argue in view of the differences between sc-uPA and tc-uPA and the previous attempts at recombinant urokinase production, the claimed process for producing tc-uPA would not be inherent to the process for sc-uPA production, even sc-uPA and tc-uPA, even though the prior art refers to both generically as urokinase. Applicants argue the claimed invention is an important achievement and the prior art processes of the conversion of sc-uPA to tc-uPA were not so efficient. Applicants' argument is not found persuasive.

There is no dispute that sc-uPA and tc-uPA are distinct molecules having distinct properties or that the claimed method achieves a level of 95% tc-uPA and not a level of 95% total urokinase, i.e., sc-uPA and tc-uPA. Also, there is no dispute that the

production of tc-uPA is important as evidenced by its use in therapeutic applications. Furthermore, there is no dispute that the prior art discloses previous attempts at recombinant production of tc-uPA. However, neither the importance of the claimed invention nor the purification of tc-uPA from sc-uPA is not at issue. Rather the issue is the obviousness of the invention in view of the references of Okabayashi et al. Zang et al. In order to clarify the record, it should be noted that none of the references in the specification, describing production of urokinase, disclose the use of butyrate as is used in the claimed process. Thus, one of ordinary skill in the art would not expect such processes to achieve the level of tc-uPA as recited in the claimed process. However, as the process of Okabayashi et al. uses a medium containing butyrate, one of skill in the art would recognize that the method of Okabayashi et al. would achieve this level of tc-uPA given a sufficient time of culturing the host cells as suggested by Zang et al.

Addressing the reference of Okabayashi et al., applicants argue: 1) the process of Okabayashi et al. discloses the exposure of the cells to butyrate for a time of not more than 24 hours; 2) butyrate treatment increased the extracellular and intracellular levels of urokinase; and 3) the urokinase assay disclosed by Okabayashi et al. does not discriminate between active and inactive urokinase and the urokinase is detected in the presence of plasminogen, a urokinase activator. Applicants conclude that the reference of Okabayashi et al. does not teach a method which meets all features of claim 81, in particular that the cells are treated with butyrate for a time of 48-200 hours and also that the method fails to achieve the desired level of tc-uPA. Applicants' argument is not found persuasive.

In response to applicant's arguments solely against the reference of Okabayashi et al., one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Regarding argument 1), while Okabayashi et al. sampled cultures usually at 24 hours (page 581), Okabayashi et al. does not teach away from longer culture times for the production of urokinase and provides no teaching that would indicate that the production of urokinase ceased after 24 hours of culturing. In this regard, it is the combination of the references that provides motivation for culturing the cells for at least up to five days to achieve a maximum level of urokinase (as suggested by Zang et al.) One of skill in the art, in view of the results of Table 2 of Okabayashi et al. (page 584) would recognize that increased culturing in the presence of butyrate would result in an increased yield of urokinase. Regarding argument 2), it is noted that, while the process of Okabayashi et al. increases the extracellular and intracellular levels of urokinase (Table 3, page 584), this is not to say that the method does not increase the level of urokinase. Thus, Okabayashi et al. does not teach away from practicing their method for a longer period of time for achieving a maximum level of urokinase as suggested by Zang et al. Regarding argument 3), it is immaterial as to whether the assay of Okabayashi et al. discriminates between sc-uPA or tc-uPA or whether the assay uses plasminogen to detect catalytically active tc-uPA. What is material is that Okabayashi et al. demonstrated that the presence of butyrate in the culture medium increased the level of urokinase and thus, a skilled artisan would have been motivated to include butyrate in

the culture medium for culturing host cells expressing urokinase. Moreover, this does not teach away from culturing the cells for an extended period of time (as clearly suggested by Table 2 of Okabayashi et al. and Zang et al.), which would have inherently resulted in the 95% level of tc-uPA as recited in the claimed process. Applicants have failed to show that the process as suggested by the combination of cited references, i.e., Okabayashi et al. AND Zang et al., does not yield the desired level of tc-uPA, i.e., applicants have failed to demonstrate an unobvious difference between the claimed process and that suggested by the prior art.

Addressing the reference of Zang et al., applicants argue Zang et al. only allows for the production of inactive sc-uPA. Applicants' argument is not found persuasive.

In response to applicant's arguments solely against the reference of Okabayashi et al., one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The combination of the references teaches a method for recombinant production of urokinase by the method of Okabayashi et al. by culturing the cells for a period of 5 days to achieve the maximum level of urokinase produced. Absent evidence to the contrary, the method suggested by the combination of references would have inherently produced tc-uPA. In this case applicants have failed to demonstrate an unobvious difference between the claimed process and that of the prior art.

Applicants argue the combination of Okabayashi et al. and Zang et al. can only suggest a process comprising the addition of butyrate and incubation of the culture for 5

days to 14 weeks, merely to achieve a stable or increased production of mainly the inactive form of urokinase. Applicants argue that the combination of references fails to suggest all features of claim 81, particularly the limitation of an incubation time from 48 to 200 hours. Applicants' argument is not found persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., an incubation time from 48 to 200 hours in claim 81) are not recited in claim 81 – only in claim 87 is this limitation present. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In this case, the combination of references provides for a method for the production of urokinase by the method of Okabayashi et al. modified by the reference of Zang et al. for a culturing time of 5 days in order to achieve the maximum level of urokinase as suggested by Zang et al. While the combination of references may not suggest a process for the production of tc-uPA at a level of 95%, it is noted that, according to MPEP 2144, "[i]t is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant." As there is clear motivation to combine the references and the method suggested by the combined references would inherently yield the desired result, it is not necessary that the prior art suggest this result, only that it achieve this result, which, absent evidence to the contrary, would be an inherent characteristic of the method suggested by the combination of the references. While applicants argue the method suggested by the combination of references would only achieve an increase in

the inactive form of urokinase, it is noted that there is no evidence of record that would support applicants' assertion and moreover, "[t]he arguments of counsel cannot take the place of evidence in the record" (MPEP 2145). In this case, applicants have failed demonstrate an unobvious difference between the claimed process and that of the prior art.

Applicants argue the motivation to combine the cited references is untenable as Okabayashi et al. teach: 1) butyrate has a growth-inhibitory effect and thus, a skilled artisan would not have cultured the cells in the presence of this toxic substance for longer than that disclosed in Okabayashi et al. and 2) the response to butyrate was rapid, which teaches away from trying to incubate cells for longer than 24 hours. Applicants argue that in view of these teachings, one of ordinary skill would not have combined the references for the purpose of achieving activation of uPA because there is no teaching to carry out such a process as the aims of the references are focused on increasing urokinase production. Applicants add that Zang et al. describes production of sc-uPA with no insight to achieve tc-uPA. Applicants further argue that a skilled artisan would not combine the cited references as there is no expectation for achieving tc-uPA at a level of 95%. Applicants argue that the rejection is based on hindsight reasoning and is not tenable. Applicants argue that this feature (although not expressly stated, "this feature" presumably refers to production of at least 95% tc-uPA) is not inherent in the method of Okabayashi et al., but has been derived from the Declaration. Applicants' argument is not found persuasive.

While the effect of butyrate on the growth of cultured cells may have been inhibitory, this nonetheless resulted in an increase in the level of urokinase produced by the cultured cells. Nowhere does Okabayashi et al. teach or suggest that butyrate should not be used in the culture of medium for recombinant urokinase production. To the contrary, the results of Okabayashi et al. clearly suggest that butyrate substantially increased the level of urokinase produced by the cells. Further, while the response was rapid, there is no teaching by Okabayashi et al. that the prolonged exposure of the cells to butyrate would result in a reduction in the level of urokinase. Instead, Okabayashi et al. teach that an increase in urokinase production was commensurate with increased time of culture (see page 584, Table 2), i.e., urokinase production is proportional to the time of culture. Thus, one of ordinary skill in the art would have been motivated to include butyrate in the cell culture medium and would have reasonably expected that increasing the culture time beyond a 24-hour period, as suggested by Zang et al., for maximum yield of urokinase, would have yielded a greater or increased level of urokinase. Again, while it is noted that, while the combination of references may not suggest a process for the production of tc-uPA at a level of 95%, it is noted that, according to MPEP 2144, "[i]t is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant." As there is clear motivation to combine the references and the method suggested by the combined references would inherently yield the desired result, it is not necessary that the prior art suggest this result, only that it achieve this result, which, absent evidence to the contrary, would be an inherent characteristic of the method suggested by the

combination of the references. In this respect, applicants have failed to demonstrate an unobvious difference between the claimed process and that of the prior art. Also, regarding the inherency of the recited limitation of at least 95% tc-uPA is produced, it is noted that the examiner has not stated this feature to be inherent in the method of Okabayashi et al., but to be an inherent feature of the method of the combination of Okabayashi et al. AND Zang et al. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). As the cited teachings are based solely on prior art disclosure and were within the level of knowledge of one of ordinary skill in the art at the time of the invention, the rejection is proper.

[12] In view of applicants' arguments, the rejection of claims 86 and 90 under 35 U.S.C. 103(a) as being unpatentable over Okabayashi et al. in view of the state of the art as represented by Zang et al. as applied to claims 81-85 and 87-89 above, and further in view of Anderson et al. (US Patent 6,506,598) is withdrawn. The reference of Anderson et al. is drawn to a method for making tPA, which is distinct from uPA and as Anderson et al. is silent as to the use of their method for the production of uPA, there is

no motivation to the combine Anderson et al. with the references of Okabayashi et al. and Zang et al.

[13] Claim 86 is rejected under 35 U.S.C. 103(a) as being unpatentable over Okabayashi et al. in view of the state of the art as represented by Zang et al. as applied to claims 81-85 and 87-89 above, and further in view of Chuppa et al. (Biotech Bioengineer 55:328-338; cited in the IDS filed December 08, 2003).

Claim 86 limits the culture temperature of the method of claim 81 to a range of 33 to 35 degrees Celsius.

Okabayashi et al. and Zang et al. disclose the teachings as described above. Neither reference teaches culturing of their respective host cell at a temperature between 33 and 35 degrees Celsius.

Chuppa et al. teach a determination of the optimal temperature for fermentation of mammalian cells for recombinant protein production. Chuppa et al. conclude that overall, reducing the fermentation temperature to 34 degrees Celsius has several advantages relative to fermentation at 35.5 or 37 degrees Celsius (page 338, left column). While Chuppa et al. teach a disadvantage of fermentation is a reduced growth rate, it is concluded that this effect on a long-term fermentation is minimal (page 338, left column).

Therefore, at the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Okabayashi et al., Zang et al., and Chuppa et al. for a method of recombinantly producing urokinase by culturing CHO cells in a serum-free medium in the presence of sodium butyrate for at least 5 days at a

temperature of 34 degrees Celsius. One would have been motivated to culture the cells at a temperature of 34 degrees Celsius because of the advantages as taught by Chuppa et al. One would have a reasonable expectation of success for a method of recombinantly producing urokinase by culturing CHO cells in a serum-free medium in the presence of sodium butyrate for at least 5 days at a temperature of 34 degrees Celsius because of the results of Okabayashi et al., Zang et al., and Chuppa et al. Therefore, claim 86, drawn to a process for the recombinant production of tc-uPA as described above would have been obvious to one of ordinary skill in the art.

[14] Claim 90 is rejected under 35 U.S.C. 103(a) as being unpatentable over Okabayashi et al. in view of the state of the art as represented by Zang et al. as applied to claims 81-85 and 87-89 above, and further in view of Paques (US Patent 5,156,967).

Claim 90 is drawn to the process of claim 88 wherein said culture medium is acidified with an acid of pH from 5 to 5.8 and optionally a non-ionic detergent is added and the culture medium is filtered.

Okabayashi et al. and Zang et al. disclose the teachings as described above. Neither reference teaches acidifying the pH of the medium following cell culture to a pH of 5 to 5.8 followed by filtering the culture medium.

Paques teaches a method for inactivating pathogenic viruses in a solution of urokinase by adjusting the pH of the solution to 5.5 with an acid, heating the solution, and sterilizing the solution by filtration (column 4, top).

Therefore, at the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Okabayashi et al., Zang et al., and

Paques for a method of recombinantly producing urokinase by culturing CHO cells in a serum-free medium in the presence of sodium butyrate for at least 5 days, collecting the culture medium, and sterilizing the culture medium by the method of Paques. One would have been motivated to sterilize the culture medium by the method of Paques in order to inactivate pathogenic viruses in the culture medium, particularly as urokinase is used as a therapeutic as evidenced by Okabayashi et al. and Zang et al. One would have a reasonable expectation of success for a method of a method of recombinantly producing urokinase by culturing CHO cells in a serum-free medium in the presence of sodium butyrate for at least 5 days, collecting the culture medium, and sterilizing the culture medium by the method of Paques because of the results of Okabayashi et al., Zang et al., and Paques. Therefore, claim 90, drawn to a process for the recombinant production of tc-uPA as described above would have been obvious to one of ordinary skill in the art.

Conclusion

[15] Status of the claims:

- Claims 81-90 are pending.
- Claims 81-90 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or

informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

05-27-04

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